Comparison of Hepatic Damage from Direct Injections of Iodinated Contrast Agents and Carbon Dioxide[1]

William C. Culp, MD
Christopher R. Mladinich, DVM, MS
Irvin F. Hawkins, Jr, MD

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Abbreviations: DSA = digital subtraction angiography, PTC = percutaneous transhepatic cholangiography, TIPS = transjugular intrahepatic portosystemic shunt

PURPOSE: This study guides the choice of contrast agent for localization of portal veins during transjugular intrahepatic portosystemic shunt (TIPS) placement or use in percutaneous transhepatic cholangiography (PTC) by providing gross anatomic and histologic comparison of effects from parenchymal injections of iodinated contrast agents and carbon dioxide.

MATERIALS AND METHODS: Eighteen New Zealand White rabbits received direct injections of 2–5 mL of either the nonionic contrast agent iohexol 300 mgI or the ionic contrast agent diatrizoate meglumine 60% into one lobe of the liver and the same volume of CO_2 into the other lobe. The rabbits were killed at 2–7 days for gross and histologic evaluation of the livers.

RESULTS: At the time of injection, the diatrizoate and iohexol sites showed persistent dark discoloration, whereas CO_2 sites showed minimal visible changes. On gross examination at death, all diatrizoate sites showed severe scarring and also commonly showed areas of necrosis. CO_2 and iohexol sites showed only minimal discoloration and needle-puncture scars ($P < .0001$). The histologic grade for diatrizoate sites was significantly more severe than paired CO_2 sites ($P < .016$). Iohexol sites showed mild histologic changes similar to paired CO_2 sites ($P = .375$).

CONCLUSION: Iohexol and CO_2 produce less severe hepatic damage and are preferred to meglumine diatrizoate for hepatic injection.

HEPATIC injections of contrast material are commonly used in two situations: as a step in transjugular intrahepatic portosystemic shunt (TIPS) procedures and in percutaneous transhepatic cholangiography (PTC). In the 1970s, wedged hepatic venography became popular as a part of liver panangiography in the workup of liver disease (1). The relative safety of modern water-soluble contrast agents such as sodium-methylglumine diatrizoate (Renografin 76; Bristol-Myers Squibb, Princeton, NJ) had been established; however, complications and side effects were also reported (2,3). Elevations of serum transaminase activity and areas of infarction were encountered; yet, the abnormal transaminase values quickly returned to normal and the hepatic damage seemed to be of little clinical significance.

With the advent of TIPS procedures in the 1990s, wedged hepatic venography experienced a revival. The most difficult part of a TIPS procedure is establishing access from the hepatic vein to the proper portion of the portal system. Numerous methods of localization of the portal vein during the procedure have been developed, but the most successful and popular one is wedged hepatic venography, either

[1] From the University of Florida Veterans Administration Medical Center, Gainesville, FL. Received March 10, 1999; revision requested April 13; revision received and accepted May 28. From the 1999 SCVIR Annual Meeting. **Address correspondence** to W.C.C., Assistant Professor of Radiology, University of Nebraska Medical Center, 600 South 42nd St., Box 981045, Omaha, NE 68198–1045; e-mail: wculp@unmc.edu.

with carbon dioxide or iodinated contrast agents (4). A variation of this is intraparenchymal injection of CO_2 from a venous approach. In PTC, a similar situation arises when iodinated contrast material is injected into the liver to locate bile ducts. Because CO_2 will not routinely identify small bile ducts well enough for PTC guidance, iodinated contrast material is required and often leads to large areas of parenchymal staining before biliary access is obtained.

Since the 1970s, new contrast agents have appeared, and their relative safety in wedged hepatic venography and intraparenchymal injections is yet to be established. The purpose of this study is to compare the damage to rabbit livers caused by intraparenchymal injections of an older ionic contrast agent, meglumine diatrizoate, (Hypaque 60; Nycomed, Princeton, NJ) with that caused by a new nonionic contrast agent of lower osmolarity, iohexol (Omnipaque 300; Nycomed), and also by CO_2, which has recently become popular as a vascular contrast agent.

MATERIALS AND METHODS

The study population consisted of 18 male and female New Zealand White rabbits, 6 months old, weighing 3.5–4.5 kg. The rabbits were obtained from an approved rabbitry and handled through an approved animal resource department. All animal research was governed by the principles of The Guide for the Care and Use of Laboratory Animals (5). The protocol was approved by the institutional Care and Use of Laboratory Animals Committee and the Veterans Affairs Medical Center subcommittee for animal studies.

The subjects were premedicated with glycopyrrolate 0.01 mg/kg subcutaneously and then induced with ketamine hydrochloride 35 mg/kg and xylazine 2.0 mg/kg intramuscularly. Anesthesia was maintained with facemask or intubation of oxygen and 1%–3% isoflurane gas to effect. The first five rabbits were placed in a supine position on a special procedures radiographic and fluoroscopic table. The abdomen was shaved and a sterile field prepared. In these rabbits, the entire procedure was performed percutaneously with confirmation of needle placement using fluoroscopic techniques. After injection of 3–5 mL of contrast agent, the sites were marked by injecting a 3-mm piece of 0.018-inch stainless steel guide wire through the 20-gauge spinal needle with the aid of a guide wire pusher. The volumes of contrast material used provided good visualization of the hepatic veins and portal vein when observed fluoroscopically. The lack of digital subtraction angiography (DSA) capability on the unit compromised detection of small amounts of each contrast agent and required larger doses for fluoroscopic imaging. The amounts used are proportionately much larger (approximately 3×) than amounts clinically used in humans. This may accentuate the changes relative to human use, and small dose testing was not performed. The small size of rabbit livers did not allow injection at three well-separated sites in each animal. Therefore, CO_2 was arbitrarily selected as a constant in all animals, and the other site that could be accommodated in the volume of the liver was randomized between iodinated contrast agents. In the last 13 rabbits, the abdomen was opened with a midline incision approximately 4 cm long and the liver was exposed. Randomization of the site either to the right or left lobe of the liver was achieved with a table of random numbers. A 21-gauge needle was placed in the designated site to a depth of 3–8 mm approximating the center of the lobe, and the iodinated contrast agent was quickly injected by hand. Volumes ranged from 2–5 mL depending on the size of the liver and its ability to contain the contrast material without visible spillage. Average volume was 3 mL. A similar volume of CO_2 was then injected using an identical technique in the other lobe. Both sites were marked for future localization with tiny tattoos. The surgical site was then closed in layers. The subjects received a prophylactic injection of 600,000 U of procaine penicillin G immediately after surgery and 24 hours later. Supportive care was administered as needed.

One rabbit was killed at 2 days after the procedure because of pneumonia; the others were killed 5–7 days after the procedure, depending on the convenience of the schedule. A necropsy was then performed on each animal, with samples from the liver obtained for gross and histopathologic examination.

The histologic samples of liver were examined microscopically for damage. The degree of injury in these samples was graded on a scale of 0–4 as previously reported (6). Grade 0 corresponded to no visible damage, and 1–4 related to increasing levels of severity of hepatocellular swelling or congestion and focal acute necrosis ranging from minimal to severe. These samples were graded by veterinary pathologists blinded to the source of the sample.

Histopathologic scores compared the paired meglumine diatrozate and CO_2 sites and the paired iohexol and CO_2 sites. The Wilcoxon rank-sum test was used.

RESULTS

The first five rabbits demonstrated the success of the technique of placing contrast material in the liver percutaneously and the success of visualizing the vascular structures with the volumes of contrast material used. However, extravasation was difficult to detect in small amounts; therefore, the abdominal cavity was opened surgically and direct visualization of the injection sites was performed in the remaining animals. At the time of direct injection, the liver was well visualized. The color at the injection site changed dramatically with each injection of either iodinated contrast material, becoming a mottled gray or black splotch 2–3 cm in diameter. This was immediately apparent and slowly faded around the periphery of the injection site during the

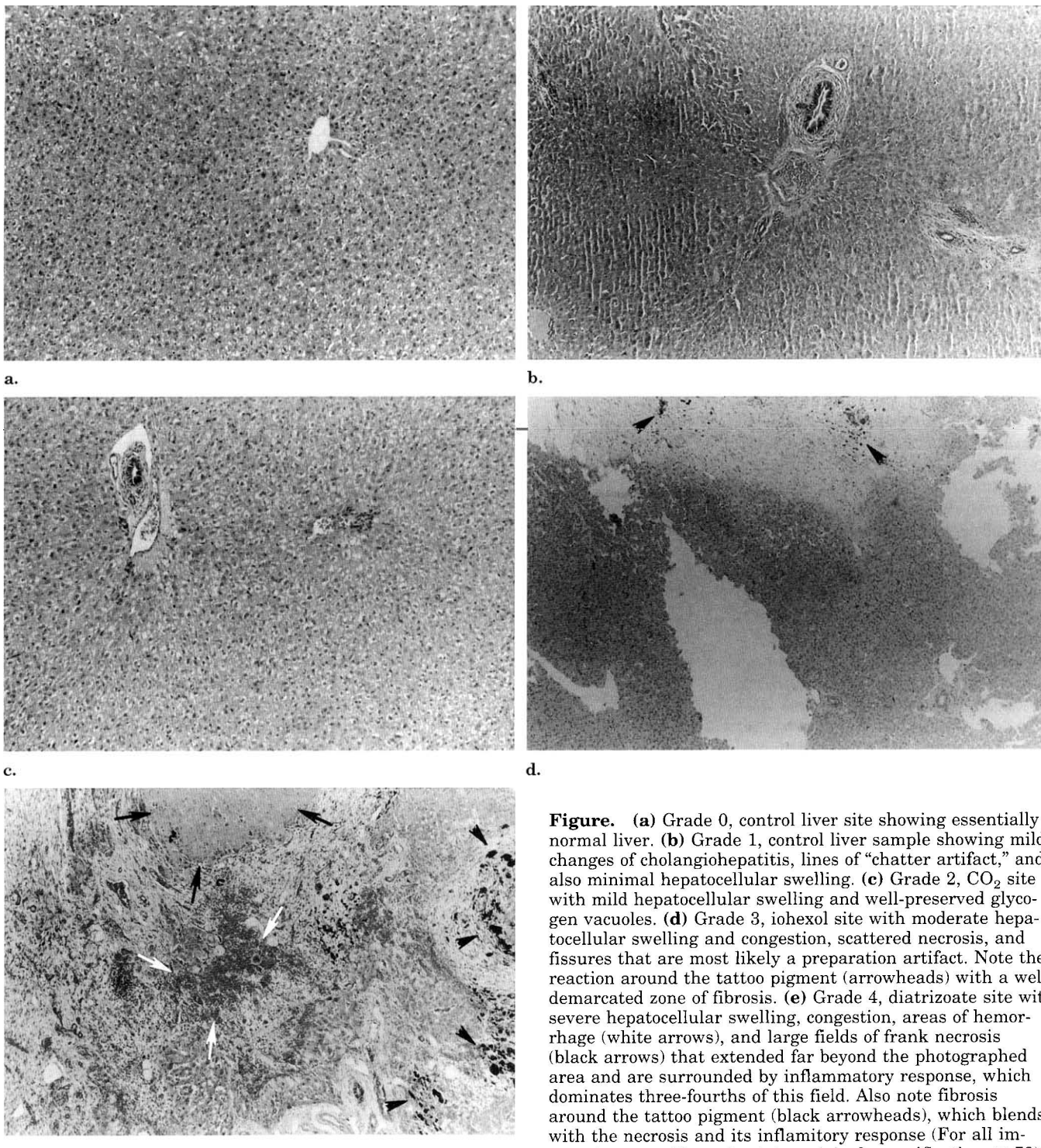

Figure. **(a)** Grade 0, control liver site showing essentially normal liver. **(b)** Grade 1, control liver sample showing mild changes of cholangiohepatitis, lines of "chatter artifact," and also minimal hepatocellular swelling. **(c)** Grade 2, CO_2 site with mild hepatocellular swelling and well-preserved glycogen vacuoles. **(d)** Grade 3, iohexol site with moderate hepatocellular swelling and congestion, scattered necrosis, and fissures that are most likely a preparation artifact. Note the reaction around the tattoo pigment (arrowheads) with a well-demarcated zone of fibrosis. **(e)** Grade 4, diatrizoate site with severe hepatocellular swelling, congestion, areas of hemorrhage (white arrows), and large fields of frank necrosis (black arrows) that extended far beyond the photographed area and are surrounded by inflammatory response, which dominates three-fourths of this field. Also note fibrosis around the tattoo pigment (black arrowheads), which blends with the necrosis and its inflamitory response (For all images, hematoxylin-eosin stain; original magnification, × 78).

next 10–20 minutes. The central portion remained generally discolored as long as the liver was visualized. In contrast, the CO_2 sites showed only minimal visual changes. Occasionally, a faint silver sheen appeared in the subcapsular area as CO_2 dissected along the surface of the liver. In most cases, there was no visible change or there was only a transient pale hue as blood was displaced from the local

vessels. In no case was there significant bleeding at the puncture site with either iodinated contrast agent or with CO_2.

At the time the rabbits were killed, the livers showed dramatic gross anatomic change at all diatrizoate sites. All 10 showed severe scarring ranging from 1 to 3 cm in diameter, with puckering of the surface of the liver and loss of volume. Frank necrosis was present in three of these areas, and in one case extended to involve the gallbladder, which was adherent to the margin of the liver at this site. The eight iohexol sites showed small areas of scarring and minimal discoloration never exceeding 1 cm in maximum dimension. Only minimal areas of volume loss were identified, and some sites were difficult to locate because of the minimal nature of the gross changes. The CO_2 sites showed even less discoloration and showed scarring consisting of only the needle puncture scar and the tattoo mark. At gross and microscopic examination, the 0.018-inch wire sites were difficult to find, whereas the tattoos were quite evident. On microscopic examination, the tattoos showed a vigorous inflammatory response that was easily differentiated from the much larger areas of change caused by the test injections.

The histologic grades **(Fig)** for diatrizoate sites and the paired CO_2 sites in the same animal showed a statistically significant difference with higher grading for the diatrizoate sites than for the CO_2 sites ($P = .016$). Iohexol sites showed no statistically significant difference in histologic grade compared to the paired CO_2 sites in the same animal ($P = .375$). The iohexol sites did show numerous areas of vacuolization, most likely a processing artifact, which appeared only rarely in the paired CO_2 sites or control sites, but actual grade levels were not sufficiently different to reach statistical significance. Sixteen of the 18 animals had chronic cholangiohepatitis in varying degrees, with control sites in the seven animals graded ranging from grade 0 to grade 2.

DISCUSSION

The occasional complications and side effects of wedged hepatic venography using small volumes of meglumine diatrizoate and sodium meglumine diatrozate contrast agents in the 1970s were usually of limited importance. Although transient derangement of liver function tests were encountered, these quickly returned to normal in most cases. Areas of persistent liver staining and hemorrhagic infarction were documented, but the great resiliency of the liver usually led to fairly prompt recovery, even in livers that were quite damaged by preexisting disease.

With the proliferation of the TIPS procedure, wedged hepatic venography became important in the localization of the main portal vein as guidance to the placement of TIPS. Better definition of the main portal vein and its major branches was required in this role than had been required in the past. This called for larger volumes of contrast material and more forceful injections. Unfortunately, when iodinated contrast agents are used, even this technique provides adequate visualization of the main portal vein in only 40% of cases (7). This failure leads to injection of even larger volumes of contrast material, which causes what appear to be more common side effects and complications. Wedged CO_2 hepatic venography or direct parenchymal injection provides a much higher success rate because of the low viscosity of the contrast agent, although its optimal imaging does require DSA rather than simple filming. The decreased inherent contrast of CO_2 does not provide good visualization without subtraction techniques, but when these are used, visualization of the main portal vein has been reported in 90%–100% of attempts (4,8).

The microcirculation of the liver is unusual in that the central vein, the portal vein, and the hepatic artery all serve a common space (1). If hepatic artery flow decreases, portal vein flow increases to compensate. If portal vein flow decreases, hepatic artery flow increases to compensate. Likewise, collaterals from hepatic artery branch to occluded hepatic artery branch are quick to develop. If one hepatic vein is occluded, flow normally shunts rapidly to a nearby alternative hepatic vein. All of these shifts can occur without major disruption of hepatic function. This anatomy allows parenchymal injections of iodinated contrast material in this common space to fill the hepatic and portal veins in many instances and allows the less viscous CO_2 to fill both almost universally. The hepatic artery is not often seen unless the needle tip actually lies in this higher pressure and structurally smaller target. Yet, direct selective catheter CO_2 injection of the hepatic artery will fill the portal and hepatic veins, whereas iodinated contrast injections here will fill only the hepatic veins (9).

In PTC applications, CO_2 can occasionally be seen in large ducts but is very difficult to see in small bile ducts without DSA. Therefore, CO_2 has little clinical use in the performance of PTC and iodinated contrast material is required. The needle tip must actually be in a biliary radicle before good filling can be obtained with either contrast agent. Otherwise, contrast material flows into various venous structures as previously described. Taking advantage of this in patients with distorted anatomy, it is sometimes helpful to inject intraparenchymal CO_2 and outline the portal veins as a guide to the bile ducts, which closely parallel them. A successful PTC often requires multiple needle passes with intermittent filling of various veins and staining of sizable areas of hepatic parenchyma before biliary access is accomplished. These stains may take many minutes to disperse and can represent large volumes of iodinated contrast material.

The volumes of contrast material used in these rabbits is proportionally larger (approximately 2–4 ×) than that required in humans for wedged veinography, in which 6–15 mL of iodinated contrast and 15–30

mL of CO_2 are usually used. A proportional dose should have been 1–1.5 mL of CO_2 and approximately half as much iodinated contrast material. However, in a pilot study, these doses did not provide fluoroscopic visualization of the portal veins (one of the protocol requirements to prove location) with the available equipment. Therefore, larger amounts were used and may have caused more severe changes than are applicable in human use. Direct comparison with PTC application is more difficult because of wide variation in injection rates, venous drainage, and volumes used in human patients.

Mechanical complications of wedged injections have been reported not only with iodinated contrast material, but also with CO_2. Hepatic lacerations have occurred and deaths have been reported with both types of contrast agents (6). As familiarity with the technique grew, sites for wedged hepatic venograms were moved from the periphery of the liver, where laceration of the capsule and lethal extravasation and bleeding have occurred, to more central locations where this risk was presumably decreased. In addition, volumes of CO_2 were decreased from 60 mL to 20–30 mL. Less vigorous injections were made, and in some centers, an occlusion balloon catheter was used to stop hepatic vein flow. More gentle injection of CO_2 in the vein on the parenchymal side of the occlusion balloon routinely gives excellent portal vein filling even without physically wedging the catheter into the paryenchyma. However, the extra catheter exchange adds complexity, consumes time, and costs several hundred dollars. The exact site of CO_2 injection does not appear to be critical, and intraparenchymal and wedged hepatic vein injections routinely provide good filling of branch and main portal veins from almost any central location.

The rabbits in our study were all specific pathogen-free quality rabbits; however, many of them had varying degrees of subclinical cholangiohepatitis at histologic examination. None of the rabbits showed gross changes at the time of injection or death related to this process, but the microscopic changes were often superimposed on those related to the contrast agents and elevated the expected grade of histiologic abnormality. This may have obscured subtle differences between CO_2 and iohexol sites. The voids in the iohexol slides are probably a technical artifact, because they have not been seen in previous studies. If they recur in future studies, they may justify a refinement of the histologic grading system. Finer gradations might successfully separate the degrees of damage caused by CO_2 and iohexol.

The experimental design allowed values to be paired within each animal and showed significantly worse grades of hepatic damage with meglamine diatrozate than with CO_2 ($P = .016$). This is consistent with early studies by Castaneda-Zuniga et al (3), which showed stellate areas of hepatic necrosis around the central veins where wedged hepatic venograms were obtained. In their study with 60% sodium meglumine diatrizoate injected at 2 mL/sec for a total volume of 6 mL in three dogs, Castaneda-Zuniga et al considered it more likely that total volume and the mechanical force of injection, rather than the osmolarity of the substance injected, were the critical factors in defining the damage. The agents of that era showed viscosities of 3.9–9.1 cP and osmolarities of 1,415–2,016 mOsm/kg. Currently, iohexol has a viscosity of 6.8 cP with an osmolarity of 709 mOsm/kg. Because the viscosity is similar and the damage as seen on histiologic sections is lower, it is suggested that osmolarity may be the more important factor in defining the level of damage to the liver. Further study of isosmolar agents, such as iodixanol (Visipaque 320; Nycomed), with an osmolarity of 290 mOsm/kg in this setting is justified. High viscosity and force of injection may play a major role in acute lacerations, but these can be rendered inconsequential by using only central locations for injection. Conversely, the very low viscosity of CO_2 contributes greatly to success in delineating the portal system. Its very nature allows it to decompress itself more rapidly in confined sites than a liquid contrast agent. At matched flow rate and volume, it should be the safest agent. Unfortunately, explosive delivery of CO_2 at very high pressure and flow can occur if the catheter is not cleared of liquid before the injection of the gas. Careful and patient low-pressure clearing of the delivery catheter or needle with CO_2 eliminates this problem. Explosive delivery of CO_2 can result in marked disruption of the tissue and may account for the cases in which microscopic damage in CO_2 sites was most marked.

Other sites where wedged venous or intraparenchymal injections may occur—peripheral tissues during venography through poor access sites, the spleen during splenoportography, the adrenal and kidney during venography, the pancreas during selective portal sampling, and so forth—do not share the rather forgiving hepatic triple vessel anatomic arrangement. The adrenal is especially at risk during excessive venous injection of iodinated contrast material, and other organs also presumably suffer damage from extravasation of contrast material. These hepatic findings may not be fully applicable to other sites that were not tested, but they suggest that nonionic agents and agents with lower osmolarity may cause less damage there. We now use only these agents or CO_2 when extravasation or retrograde intraparenchymal flow is a concern.

In summary, meglumine diatrizoate should not be used for wedged hepatic venography or PTC applications and all hyperosmolar contrast agents may be suspected of causing hepatic damage. Intraparenchymal CO_2 is now our contrast agent of choice for visualization of hepatic veins and portal vessel anatomy at the time of TIPS placement. When iodinated contrast material is required to solve a specific question in TIPS placement or when PTC is performed, iohexol is recommended to avoid the localized damage caused by meglumine diatrizoate. It

is possible that even better contrast agents are available, and further study of isosmolar agents such as iodixanol could be justified.

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Erratum

Please note the following corrections to the September article entitled "Recommended Reporting Standards for Vena Caval Filter Placement and Patient Follow-up," JVIR 1999; 10:1013–1019. The authors should be: Participants in the Vena Caval Filter Consensus Conference, April 13–14, 1998, Chicago, Illinois.

The Addendum in this article should read as follow:

Addendum

The Participants in the Vena Caval Consensus Conference were: Dr. Joseph Bonn, Department of Radiology, Thomas Jefferson University; Dr. Kyung J. Cho*, Department of Radiology, University of Michigan; Dr. Mark Cipolle, Department of Surgery, Lehigh Valley Hospital; Dr. Ernest Ferris, Department of Radiology, University of Arkansas; Dr. Stuart Geller, Department of Radiology, Massachusetts General, Harvard University; Dr. Clement Grassi, Department of Radiology, Harvard Medical School; Dr. Lazar J. Greenfield*, Department of Surgery, University of Michigan; Dr. Michael Lilly, Department of Surgery, University of Maryland; Dr. Timothy C. McGowan*, Department of Radiology, University of Nebraska; Dr. David McFarland*, Department of Radiology, University of Arkansas; Dr. Stephen Okhi, Department of Radiology, University of Maryland; Dr. S. Osher Pais, Department of Radiology, University of Maryland; Ms. Mary C. Proctor*, Department of Surgery, University of Michigan; Dr. John-Baptiste Ricco, Department of Surgery, University of Poitiers; Dr. Robert B. Rutherford, Department of Surgery, University of Colorado; Dr. Morris Simon, Department of Radiology, Beth Israel Deaconess, Harvard University; Dr. Anthony Venbrux, Department of Radiology, Johns Hopkins University; and Dr. Robert Vogelzang, Department of Radiology, Northwestern University.

* Indicates members of the Organizing Committee.